

What we claim is:

1. An apparatus for the controlled automated performance of polymerase chain reactions in at least one sample tube containing a known volume of a liquid sample mixture, which apparatus comprises:

a. a sample block having at least one well for said at least one sample tube,

b. a computing apparatus,

c. heating and cooling means controlled by said computing apparatus for changing the temperature of said sample block, and

d. means for determining the temperature of said block in a first sample interval, wherein said first sample interval is an interval of time designated as time n;

wherein said computing apparatus includes means for determining the temperature of said liquid sample mixture as a function of the temperature of said sample block over time.

2. The apparatus of claim 1, wherein said computing apparatus includes means for determining said sample temperature in said first sample interval according approximately to:

$$T_{\text{samp}_n} = T_{\text{samp}_{n-1}} + (T_{B_n} - T_{\text{samp}_{n-1}}) * t_{\text{interval}}/\tau$$

where $T_{\text{sample } n}$ is equal to the sample temperature in said first sample interval, $T_{\text{sample } n-1}$ is a sample temperature in a second sample interval immediately preceding the first sample interval, said second sample interval designated as time $n-1$, T_b is equal to the block temperature in said first sample interval, t_{interval} is a time in seconds between consecutive sample intervals, and τ is a function of thermal characteristics of said apparatus.

3. The apparatus of claim 2, wherein said thermal characteristics comprise a first thermal time constant corresponding to said at least one sample tube and said volume of said sample mixture, and a second thermal time constant corresponding to a block temperature sensor thermally coupled to said block.

4. The apparatus of claim 3, wherein τ equals approximately said first thermal time constant minus said second thermal time constant.

5. The apparatus of claim 4, wherein said first thermal time constant is between approximately 5 seconds and 14 seconds and said second thermal time constant equals approximately 1.5 seconds.

6. The apparatus of claim 2 further comprising an input device for receiving one or more user defined setpoints, each said setpoint defining a hold time / first temperature pair; and

wh rein said computing apparatus includes means for controlling said heating and cooling means as a function of said user d fined setpoints and said sample temperature; and wherein said computing apparatus further comprises means to combine one or more setpoints in a user defined order to form a profile wherein the controlling of said heating and cooling means as a function of the setpoints in a said profile defines a profile run.

7. The apparatus of claim 6, wherein said first temperature defines a target sample temperature after ramping said sample temperature at a preselected ramp rate, and said hold time defines a length of time to maintain said sample at said first temperature after ramping.

8. The apparatus of claim 1 further including an input device for receiving user defined setpoints defining a hold time/temperature profile, wherein said computing apparatus includes means for controlling said heating and cooling means as a function of said user defined setpoints and said sample temperature.

9. The apparatus of claim 7, wherein said apparatus for the controlled automated performance of polymerase chain reactions includes an enclosure for said sample block defining an enclosed ambient atmosphere, and wherein said sample block is comprised of a central region containing in an upper surface an array of sample wells for holding said at least one sample tube,

an end edge region comprising two end edges at opposite ends of said block which are in thermal contact with said enclosed ambient atmosphere, and a manifold region comprising two manifold edges at opposite sides of said block, wherein each said manifold edge is thermally coupled to a manifold.

10. The apparatus of claim 9 wherein said heating means is a heater having a central heating zone thermally coupled to said central region, an end edge heating zone thermally coupled to said edge region, and a manifold heating zone thermally coupled to said manifold region.

11. The apparatus of claim 10 wherein said computing apparatus comprises means for determining an actual heating power to be applied to each said heating zone in said first sample interval, including:

a. means for determining a theoretical second power representing the total power to apply to said block in said sample interval without accounting for power losses,

b. means for determining theoretical third powers to be applied to each said zone in said first sample interval as a function of said theoretical second power,

c. means for determining power losses by said regions in said first sample interval, and

d. means for determining the actual heating power to be applied to each said heating zone as a function of said theoretical third powers and said power losses by said regions.

12. The apparatus of claim 11, wherein said means for determining said theoretical second power includes:

a. means for determining a first fraction of the difference between the target sample temperature after ramping and the sample temperature in said second sample interval to be made up in said first sample interval, and

b. means for determining said theoretical second power as a function of said first fraction, said sample temperature in said second sample interval and said block temperature in said second sample interval.

13. The apparatus of claim 12 wherein said means for determining said theoretical second power includes means for determining said theoretical second power as a function of:

$$CP * P/t_{\text{interval}} * ((SP - T_{\text{sample}_{n-1}}) * F * \tau/t_{\text{interval}} + T_{\text{sample}_{n-1}} - T_{B_{n-1}})$$

where CP is equal to a thermal mass of said block, P is a proportional term gain, SP is said target sample temperature after ramping, F is said first fraction and $T_{B_{n-1}}$ is equal to the temperature of the block in said second sample interval.

14. The apparatus of claim 11 wherein said computing apparatus comprises means for adjusting said theoretical second power when said sample temperature in said second sample interval

is within an integral band of said target sample temperature after ramping, in order to close out remaining error.

15. The apparatus of claim 14, wherein said integral band is approximately $\pm 0.5^{\circ} \text{C}$.

16. The apparatus of claim 14, wherein said means for adjusting said theoretical second power comprises means for adjusting said theoretical second power as a function of a power adjustment term given approximately by:

$$\text{int_sum}_n = \text{int_sum}_{n-1} + (\text{SP} - T_{\text{sample}_{n-1}})$$

$$\text{pwr_adj} = k_i * \text{int_sum}_n$$

where pwr_adj equals said power adjustment term, int_sum_n is a value of an accumulating integral term in said first sample interval, int_sum_{n-1} is a value of said accumulating integral term in said second sample interval, SP is said target sample temperature after ramping, and k_i equals an integral gain.

17. The apparatus of claim 16, wherein said integral gain is approximately 512.

18. The apparatus of claim 11, wherein said means for determining said theoretical third powers comprises means for dividing said theoretical second power into said theoretical third powers in proportion to the relative areas of said zones.

19. The apparatus of claim 11, wherein said means for determining power losses by said regions in said first sample interval comprises:

- a. means for determining power lost to a foam backing on said sample block in said first sample interval,
- b. means for determining power lost to said manifolds in said first sample interval, and
- c. means for determining power lost to said enclosed ambient atmosphere in said first sample interval.

20. The apparatus of claim 19, wherein said means for determining power lost to said foam backing on said sample block in said first sample interval comprises:

- a. means for determining the temperature of said foam backing in said first sample interval,
- b. means for determining said power lost to said foam backing as a function of said temperature of said foam backing in said first sample interval, said temperature of said block in said first sample interval, and a thermal mass of said foam backing.

21. The apparatus of claim 20, wherein said means for determining the temperature of the foam backing in said first sample interval comprises means for determining the temperature of the foam backing in said first sample interval according approximately to:

$$T_{\text{foam}_n} = T_{\text{foam}_{n-1}} + (T_{B_n} - T_{\text{foam}_{n-1}}) * t_{\text{interval}} / \text{tau2}$$

where T_{foam_n} is equal to the temperature of the foam backing in said first sample interval, $T_{\text{foam}_{n-1}}$ is equal to the foam backing temperature in said second sample interval, and tau2 is a function of said thermal mass of said foam backing.

22. The apparatus of claim 21, wherein tau2 is approximately 30.

23. The apparatus of claim 20, wherein said means for determining the power lost to said foam backing comprises means for determining the power lost to said foam backing according approximately to:

$$\text{foam-pwr} = C * (T_{B_n} - T_{\text{foam}_n})$$

where foam-pwr is said power lost to said foam backing in said first sample interval, T_{foam_n} is equal to the temperature of the foam in said first sample interval and C is equal to the thermal mass of the foam backing.

24. The apparatus of claim 19 additionally comprising means for delivering a bias coolant constantly applied to said sample block, and wherein said means for determining the power lost to said manifolds in said first sample interval comprises means for

determining the power lost to said manifolds in said first sample interval according approximately to:

$$\text{manifold_loss} = KA (T_{B_n} - T_{A_n}) + KC (T_{B_n} - T_{C_n}) + TM (dT/dt)$$

where manifold_loss equals said power lost to said manifolds in said first sample interval, KA equals an end edge region-to-enclosed ambient atmosphere conductance constant, T_{A_n} equals the enclosed ambient atmosphere temperature in said first sample interval, T_{C_n} equals the temperature of said bias coolant in said first sample interval, KC equals a sample block-to-coolant conductance constant, TM equals a thermal mass of said manifolds and dT/dt equals said preselected ramp rate.

25. The apparatus of claim 19 additionally comprising means for delivering a bias coolant constantly applied to said sample block, and wherein said means for determining the power lost to said enclosed ambient atmosphere in said first sample interval comprises means for determining the power lost to said enclosed ambient atmosphere in said first sample interval according approximately to:

$$\text{ambient_loss} = K2A (T_{B_n} - T_{A_n}) + K2C (T_{B_n} - T_{C_n}) + TM2(dT/dt)$$

where ambient_loss is said power lost to said enclosed ambient atmosphere in said first sample interval, K2A equals an end edge region-to-enclosed ambient atmosphere conductance constant, T_{A_n} equals the enclosed ambient atmosphere temperature in said first sample interval, K2C equals an end edge region-to-coolant conductance constant, T_{c_n} equals the temperature of the bias coolant in said first sample interval, TM2 equals a thermal mass of said enclosed ambient atmosphere, and dT/dt equals said preselected ramp rate.

26. The apparatus of claim 11, wherein said means for determining the actual heating power to be applied to each said heating zone as a function of said theoretical third powers and said power losses by said regions comprises means for determining the actual heating power to be applied to each said heating zone as a function of said theoretical third powers and said power losses by said regions according approximately to:

$$\begin{aligned}\text{central_pwr} &= \text{pwr} * \text{cper} \\ \text{manifold_pwr} &= \text{pwr} * \text{mper} + \text{manifold_loss} \\ \text{edge_pwr} &= \text{pwr} * \text{eper} + \text{ambient_loss}\end{aligned}$$

where pwr is a function of said theoretical second power plus power lost to a foam backing on said block in said first sample interval, manifold_loss equals a power lost to said manifolds in said first sample interval, ambient_loss equals a power lost in

said edge region to said enclosed ambient atmosphere in said first sample interval, $central_pwr$ equals a power to be applied to said central heating zone in said first sample interval, $manifold_pwr$ equals a power to be applied to said manifold heating zone in said first sample interval, $edge_pwr$ equals a power to be applied to said end edge heating zone in said first sample interval, $cper$ equals a percentage of heater area in said central heating zone, $mper$ equals a percentage of heater area in said manifold heating zone, and $eper$ equals a percentage of heater area in said edge heating zone.

27. The apparatus of claim 26, wherein $cper$ equals approximately .66, $mper$ equals approximately .20 and $eper$ equals approximately .14.

28. The apparatus of claim 9, wherein said sample block contains multiple transverse bias cooling channels alternating with multiple transverse ramp cooling channels, said bias and ramp cooling channels being parallel to said upper surface, said apparatus further comprising means for constantly pumping chilled coolant through said bias cooling channels and means for selectively pumping chilled coolant through said ramp cooling channels comprising valve means controlled by said computing apparatus.

29. The apparatus of claim 28 wherein said computing apparatus comprises means for determining a total cooling power

to be applied to said block in said first sample interval including:

- a. means for determining a theoretical cooling power representing the total power to apply to said block in said first sample interval without accounting for power losses,
- b. means for determining power losses in said block regions in said first sample interval, and
- c. means for determining said total cooling power as a function of said theoretical cooling power and said power losses.

30. The apparatus of claim 29 wherein said means for selectively pumping chilled coolant through said ramp cooling including further comprises:

- a. means for determining that ramp direction is downward,
- b. means for determining a cooling breakpoint as a function of said block temperature and a temperature of said coolant, and
- c. means for determining if coolant will be pumped through said ramp cooling channels as a function of said total cooling power and said cooling breakpoint, wherein the determination made by said means for determining if coolant will be pumped through said ramp cooling channels constitutes a ramp cooling decision.

31. The apparatus of claim 29 wherein said means for determining said theoretical cooling power includes:

a. means for determining a second fraction of the difference between the target sample temperature after ramping and the sample temperature in said second sample interval to be made up in said first sample interval, and

b. means for determining said theoretical cooling power as a function of said second fraction, said sample temperature in said second sample interval and said block temperature in said second sample interval.

32. The apparatus of claim 31, wherein said means for determining said theoretical cooling power comprises means for determining said theoretical cooling power as a function of:

$$CP * P/t_{interval} * ((SP - T_{s_{amp_{n-1}}}) * F * tau/t_{interval} + T_{s_{amp_{n-1}}} - T_{B_{n-1}})$$

where CP is equal to a thermal mass of said block, P is a proportional term gain, SP equals said target sample temperature after ramping, $T_{B_{n-1}}$ is equal to the temperature of the block in said second sample interval, F is said second fraction and $T_{s_{amp_{n-1}}}$ is equal to the temperature of the block in said second sample interval.

33. The apparatus of claim 29 wherein said computing apparatus comprises means for adjusting said theoretical cooling power when said sample temperature in said second sample interval

is within an integral band of said targ t sample temperature after ramping, in order to close out remaining error.

34. The apparatus of claim 33, wherein said integral band is approximately $\pm 0.5^{\circ} \text{C}$.

35. The apparatus of claim 33 , wherein said means for adjusting said theoretical cooling power comprises means for adjusting said theoretical cooling power as a function of a power adjustment term given approximately by:

$$\begin{aligned} \text{int_sum}_n &= \text{int_sum}_{n-1} + (\text{SP} - \text{T}_{\text{temp}_{n-1}}) \\ \text{pwr_adj} &= k_i * \text{int_sum}_n \end{aligned}$$

where pwr_adj equals said power adjustment term, int_sum_n is a value of an accumulating integral term in said first sample interval, int_sum_{n-1} is a value of said accumulating integral term in said second sample interval, SP equals said target sample temperature after ramping, and k_i equals an integral gain.

36. The apparatus of claim 35, wherein said integral gain is approximately 512.

37. The apparatus of claim 29, wherein said means for determining power losses in said block regions in said first sample interval comprises:

a. means for determining power lost to a foam backing on said sample block in said first sample interval

b. means for determining power lost to said manifolds in said first sample interval, and

c. means for determining power lost to said enclosed ambient atmosphere in said first sample interval.

38. The apparatus of claim 37, wherein said means for determining power lost to said foam backing on said sample block in said first sample interval comprises:

a. means for determining the temperature of said foam backing in said first sample interval,

b. means for determining said power lost to said foam backing as a function of said temperature of said foam backing in said sample interval, said temperature of said block in said first sample interval, and a thermal mass of said foam backing.

39. The apparatus of claim 38, wherein said means for determining the temperature of the foam backing in said first sample interval comprises means for determining the temperature of the foam backing in said first sample interval according approximately to:

$$T_{\text{foam}_n} = T_{\text{foam}_{n-1}} + (T_{B_n} - T_{\text{foam}_{n-1}}) * t_{\text{interval}} / \tau^2$$

where T_{foam_n} is equal to the temperature of the foam backing in said first sample interval, $T_{\text{foam}_{n-1}}$ is equal to the foam backing

temperature in said second sample interval, and tau2 is a function of said thermal mass of said foam backing.

40. The apparatus of claim 39, wherein tau2 is approximately 30.

41. The apparatus of claim 39, wherein said means for determining the power lost to said foam backing comprises means for determining the power lost to said foam backing according approximately to:

$$\text{foam-pwr} = C * (T_{B_n} - T_{\text{foam}_n})$$

where foam-pwr is said power lost to said foam backing in said first sample interval, T_{foam_n} is equal to the temperature of the foam in said first sample interval and C is equal to the thermal mass of the foam backing.

42. The apparatus of claim 37, wherein said means for determining the power lost to said manifolds in said first sample interval comprises means for determining the power lost to said manifolds in said first sample interval according approximately to:

$$\text{manifold_loss} = KA (T_{B_n} - T_{A_n}) + KC (T_{B_n} - T_{C_n}) + TM (dT/dt)$$

where manifold_loss equals said power lost to said manifolds in said first sample interval, KA equals an end edge region-to-enclosed ambient atmosphere conductance constant, T_{A_n} equals the enclosed ambient atmosphere temperature in said first sample interval, T_{c_n} equals a temperature of said bias coolant in said first sample interval, KC equals a sample block-to-coolant conductance constant, TM equals a thermal mass of said manifolds and dT/dt equals said preselected ramp rate.

43. The apparatus of claim 37, wherein said means for determining the power lost to said enclosed ambient atmosphere in said first sample interval comprises means for determining the power lost to said enclosed ambient atmosphere in said first sample interval according approximately to:

$$\text{ambient_loss} = K2A (T_{B_n} - T_{A_n}) + K2C (T_{B_n} - T_{c_n}) + TM2(dT/dt)$$

where ambient_loss is said power lost to said enclosed ambient atmosphere in said first sample interval, K2A equals an end edge region-to-enclosed ambient atmosphere conductance constant, T_{A_n} equals the enclosed ambient atmosphere temperature in said first sample interval, K2C equals an end edge region-to-coolant constant, T_{c_n} equals the coolant temperature in said first sample interval, TM2 equals a thermal mass of said enclosed ambient atmosphere, and dT/dt equals said preselected ramp rate.

44. The apparatus of claim 30, wherein said cooling breakpoint is a function of the difference between said block temperature in said first sample interval and said temperature of said coolant fluid in said first sample interval.

45. The apparatus of claim 30, wherein said means for determining if said ramp cooling channels will be open further comprises means for determining if said ramp cooling channels will be open as a function of the difference between said total cooling power and said cooling breakpoint.

46. The apparatus of claim 1, further comprising means for overshooting the temperature of said sample block above a desired sample temperature, thereby decreasing an upramp time required for said liquid sample mixture to achieve said desired sample temperature.

47. The apparatus of claim 46 further comprising means for controlling the overshoot such that it is equal to or less than approximately 0.5° C.

48. The apparatus of claim 16 additionally comprising means for delivering a bias coolant constantly applied to said sample block, and wherein said means for adjusting said theoretical second power comprises means for dynamically modifying said integral gain when said sample temperature is within said

integral band of said target sample temperature, and said apparatus is performing an upramp, according approximately to:

$$\text{Gain}_n = C1 * (\text{SP} - \text{TC}_n) + C2$$

Where Gain_n is said integral gain in said first sample interval, $C1$ is a first gain constant, SP is said target sample temperature after ramping, TC_n is the temperature of said coolant in said first sample interval and $C2$ is a second gain constant.

49. The apparatus of claim 48, wherein said $C1$ equals approximately 0.65.

50. The apparatus of claim 48, wherein said $C2$ equals approximately 109.

51. The apparatus of claim 48, wherein said $C2$ equals approximately 105.

52. The apparatus of claim 48 wherein a gain constant is used for said integral gain when said sample temperature is within a second integral band of said target sample temperature, said second integral band being smaller than said integral band.

53. The apparatus of claim 52, wherein said integral band is approximately $\pm 11^\circ\text{C}$ and said second integral band is approximately $\pm 0.5^\circ\text{C}$.

54. The apparatus of claim 52, wherein said gain constant is approximately 512.

55. The apparatus of claim 1, further comprising means for undershooting the temperature of said sample block below a desired sample temperature, thereby decreasing a downramp time required for said liquid sample mixture to achieve said desired sample temperature.

56. The apparatus of claim 55 further comprising means for controlling the undershoot such that it is equal to or less than approximately 0.5° C.

57. The apparatus of claim 30 further comprising means for dynamically changing said means for determining said theoretical cooling power such that the temperature of the block will undershoot said target sample temperature after ramping in a controlled fashion.

58. The apparatus of claim 57 further comprising means for activating, as a function of said target sample temperature after ramping, ramp direction, and said ramp cooling decision, said means for dynamically changing said means for determining said theoretical cooling power.

59. The apparatus of claim 58, wherein said means for activating said means for dynamically changing said means for determining said theoretical cooling power comprises means for activating said means for dynamically changing said means for determining said theoretical cooling power if said target sample temperature after ramping is greater than approximately 45° C, ramp direction is downward and said ramp cooling decision is not to ramp.

60. The apparatus of claim 57, wherein said means for dynamically changing said means for determining said theoretical cooling power further comprises means for determining said theoretical cooling power as a function of:

$$CP = P/t_{interval} * ((SP - T_{B_{n-1}}) * F * \tau/t_{interval})$$

61. The apparatus of claim 1, wherein said means for determining the temperature of said block in said first sample interval comprises means for determining the temperature of said block in said first sample interval as a function of at least one temperature of said block in a previous sample interval.

62. The apparatus of claim 1, wherein said means for determining the temperature of said block in said first sample interval comprises means for reading the temperature of said block from a block temperature sensor thermally coupled to said block.

63. The apparatus of claim 2, wherein t_{interval} equals approximately 0.2 seconds.

64. The apparatus of claim 1, wherein said known volume of liquid sample mixture is in the range of approximately 20-100 microliters.

65. In an apparatus comprising a servomechanism, the improvement comprising means for dynamically adjusting gain to compensate for dynamic changes in damping.

66. In an apparatus comprising a temperature control servo system, the improvement comprising means for dynamically adjusting gain to compensate for dynamic changes in damping.

67. The apparatus of claim 6, wherein said computing apparatus comprises means for receiving user issued commands to invoke said profile runs, wherein said invoking causes said profiles to be run at least once.

68. The apparatus of claim 67, wherein said input device further comprises means for receiving a user defined cycle count number for a plurality of said profiles, and wherein said computing means comprises means for running said profiles said cycle count number of times automatically when said profiles are invoked.

69. The apparatus of claim 68, wherein said computing apparatus further comprises means for linking multiple profiles in any order to form a protocol, said protocol defining a sequence of said profiles to be invoked automatically upon said command from the user, wherein invoking said sequence of profiles automatically defines a protocol run.

70. The apparatus of claim 69, wherein said computing apparatus further comprises means for linking a single profile a plurality of times in a single protocol.

71. The apparatus of claim 69, wherein said computing apparatus further comprises means for storing a plurality of protocols.

72. The apparatus of claim 71, wherein said computing apparatus comprises means for including any said profile in a plurality of said protocols.

73. The apparatus of claim 69, wherein said computing apparatus comprises means for protecting a profile included in any said protocol from being deleted or overwritten.

74. The apparatus of claim 6, further comprising means for determining that an electrical power to operate said apparatus went off during a said profile run.

75. The apparatus of claim 74 further comprising means for reporting the length of said electrical power outage when said electrical power is restored.

76. The apparatus of claim 74, further comprising means for automatically starting a soak of said liquid sample mixture upon restoration of said electrical power.

77. The apparatus of claim 76, wherein said soak occurs at approximately 4°C.

78. The apparatus of claim 68 further comprising means for automatically increasing the hold time of any or all said setpoints from cycle to cycle in said cycle count.

79. The apparatus of claim 78, wherein activation of said means for automatically increasing the hold time of any or all setpoints from cycle to cycle is selectable as a user level option.

80. The apparatus of claim 78, wherein said computing apparatus comprises means for receiving first user defined values defining an increment in hold time from cycle to cycle, and wherein said means for automatically increasing the hold time comprises means for automatically increasing the hold time of any

or all said setpoints from cycle to cycle as a first function of said first user defined values.

81. The apparatus of claim 80, wherein said first function is a linear function.

82. The apparatus of claim 80, wherein said first function is a geometric function.

83. The apparatus of claim 68 further comprising means for automatically decreasing the hold time of any or all said setpoints from cycle to cycle in said cycle count.

84. The apparatus of claim 83, wherein activation of said means for automatically decreasing the hold time of any or all setpoints from cycle to cycle is selectable as a user level option via said input device.

85. The apparatus of claim 83, wherein said computing apparatus comprises means for receiving second user defined values defining a decrement in hold time from cycle to cycle, and wherein said means for automatically decreasing the hold time comprises means for automatically decreasing the hold time of any or all said setpoints from cycle to cycle as a second function of said second user defined values.

86. The apparatus of claim 85, wherein said second function is a linear function.

87. The apparatus of claim 85, wherein said second function is a geometric function.

88. The apparatus of claim 68 further comprising means for automatically increasing the first temperature of any or all said setpoints from cycle to cycle in said cycle count.

89. The apparatus of claim 88, wherein activation of said means for automatically increasing the first temperature of any or all setpoints from cycle to cycle is selectable as a user level option.

90. The apparatus of claim 88, wherein said computing apparatus comprises means for receiving third user defined values defining an increment in the first temperature from cycle to cycle, and wherein said means for automatically increasing the first temperature comprises means for automatically increasing the first temperature of any or all setpoints from cycle to cycle as a third function of said third user defined values.

91. The apparatus of claim 90, wherein said third function is a linear function.

92. The apparatus of claim 90, wherein said third function is a geometric function.

93. The apparatus of claim 68 further comprising means for automatically decreasing the first temperature of any or all said setpoints from cycle to cycle in said cycle count.

94. The apparatus of claim 93, wherein activation of said means for automatically decreasing the first temperature of any or all setpoints from cycle to cycle is selectable as a user level option.

95. The apparatus of claim 93, wherein said computing apparatus comprises means for receiving fourth user defined values defining a decrement in first temperature from cycle to cycle, and wherein said means for automatically decreasing the first temperature comprises means for automatically decreasing the first temperature of any or all setpoints from cycle to cycle as a fourth function of said fourth user defined values.

96. The apparatus of claim 95, wherein said fourth function is a linear function.

97. The apparatus of claim 95, wherein said fourth function is a geometric function.

98. The apparatus of claim 69, further comprising a programmed pause option means to automatically suspend a said profile run for a user defined period of time.

99. The apparatus of claim 98, further comprising a programmed pause option means to automatically suspend a said protocol run for a user defined period of time.

100. The apparatus of claim 99, wherein said pause option means comprises means to suspend a said profile run at any point in a said profile run or during any or all cycles of a said profile invocation, and further comprising means for suspending a said protocol run after any or all said profile runs in a said protocol run.

101. The apparatus of claim 7 further comprising user-controllable means for defining a temperature range such that said computing apparatus will commence timing said hold time when said sample temperature is within said temperature range of said target sample temperature.

102. The apparatus of claim 3, further comprising an input device for receiving a tube type and a reaction volume, and wherein said computing apparatus comprises means for determining said thermal time constant for said reaction tube as a function of said tube type and said reaction volume.

103. The apparatus of claim 10, further comprising means for performing diagnostic checks of said heating means.

104. The apparatus of claim 103, wherein said diagnostic checks of said heating means comprises one or more heater ping tests, block thermal capacity tests, ramp cooling conductance tests, sensor lag tests.

105. The apparatus of claim 33, further comprising means for performing diagnostic checks of a cooling capacity of said apparatus.

106. The apparatus of claim 28, wherein said diagnostic checks comprise one or more control cooling conductance tests, block thermal capacity tests, chiller tests, ramp cooling conductance tests, sensor lag tests, coolant capacity tests.

107. The apparatus of claim 1, further comprising means for performing hardware diagnostics on user demand and/or automatically upon system start-up.

108. The apparatus of claim 107, wherein said hardware diagnostics include tests of one or more of a Programmable Peripheral Interface device, Battery RAM device, Battery RAM checksum, EPROM devices, Programmable Interface Timer devices, Clock/Calendar device, Programmable Interrupt Controller device, Analog to Digital Section, RS-232 Section, Display Section,

Keyboard, Beeper, Ramp Cooling Values, EPROM mismatch, Firmware version level, Battery RAM Checksum and Initialization, Autostart Program Flag, Clear Calibration Flag, Heated Cover heater and control circuitry, Edge heater and control circuitry, Manifold heater and control circuitry, Central heater and control circuitry, Sample block thermal cutoff, Heated cover thermal cutoff.

109. The apparatus of claim 62 further means for adjusting temperature sensor readings from said block temperature sensor to account for drift in analog circuitry.

110. The apparatus of claim 109 wherein said means for adjusting temperature sensor readings from said block temperature sensor to account for drift in the analog circuitry further comprises means for determining said drift according to:

- a) Measuring one or more test voltages under controlled conditions,
- b) Reading said voltages at the start of each run
- c) Measuring said drift as a function of said test voltages under controlled conditions and said voltages at the start of each run.

111. The apparatus of claim 69, wherein said computing apparatus comprises a means to display the approximate amount of time left in a said profile run or in a said protocol run.

112. The apparatus of claim 69, wherein said computing apparatus comprises means for displaying, during a said profile or protocol run, the sample temperature at any given time in said profile or protocol run.

113. The apparatus of claim 7, further comprising means for determining, for one or more setpoints, a first difference between said sample temperature after said hold time has expired and said target sample temperature of said setpoint.

114. The apparatus of claim 113, further comprising means for receiving and storing a user defined temperature differential.

115. The apparatus of claim 114, wherein said computing apparatus comprises means to report an error if said user defined temperature differential is greater than said first difference.

116. The apparatus of claim 7, further comprising means for configuring a second temperature, and further comprising means for causing said heating and cooling means to maintain said sample at said second temperature during any idle state.

117. The apparatus of claim 7, further comprising means for determining that, for one or more setpoints, said first temperature is reached within a user definable amount of time.

118. The apparatus of claim 93, further comprising means for determining whether said automatically decreased first temperature remains within a defined range.

119. The apparatus of claim 88, further comprising means for determining whether said automatically increased first temperature remains within a defined range.

120. The apparatus of claim 83, further comprising a means to determine whether said automatically decreased hold time is negative.

121. The apparatus of claim 62 further comprising means to continually monitor said block sensor and to invoke an abort procedure if block sensor readings are above a maximum desirable temperature for said block by a predetermined number of degrees for a predetermined number of times.

122. The apparatus of claim 121, wherein said abort procedure comprises one or more of aborting the profile or protocol run, flagging an error in a history file, displaying message alerts to a user, disabling said heating means.

123. The apparatus of claim 69, further comprising means for printing information stored in said system.

124. The apparatus of claim 123, wherein said information comprises one or more of: contents of a profile, contents of a protocol, listing of created profiles, listing of created protocols, configuration parameters, system calibration parameters.

125. The apparatus of claim 1, further comprising means for controlling all user controllable functions remotely.

126. The apparatus of claim 1 wherein said computing apparatus comprises means to display a menu driven user interface.

127. The apparatus of claim 69 wherein said computing apparatus maintains a history file of an immediately previous run containing details of said previous run suitable for integrity checks and error analysis.

128. A method for computer control of the automated performance of polymerase chain reactions in at least one sample tube containing a known volume of liquid sample mixture by means of a computer-controlled thermocycler including a computing apparatus, a sample block having at least one well for said at least one sample tube, a block temperature sensor thermally

coupled to said sample block, and heating and cooling means controlled by said computing apparatus for changing the temperature of said sample block, comprising the steps by said computing apparatus of

- a. reading the block temperature at predetermined times,
- b. determining the temperature of said liquid sample mixture as a function of the temperature of said sample block over time, and
- c. controlling said heating and cooling means as a function of said sample temperature.

129. The method according to claim 128 wherein said step of determining the temperature of said liquid sample comprises the steps of

(i) determining a first thermal time constant for said at least one sample tube and said volume of liquid sample mixture,

(ii) determining a second thermal time constant for said block temperature sensor, and

(iii) determining the sample temperature in a sample interval at a current time n according to the formula

$$T_{\text{samp}_n} = T_{\text{samp}_{n-1}} + (T_{B_n} - T_{\text{samp}_{n-1}}) * t_{\text{interval}}/\tau$$

where T_{samp_n} is equal to the sample temperature at time n, the time at said current sample interval, $T_{\text{samp}_{n-1}}$ is equal to the sample temperature at an immediately preceding sample interval having

occurred at time $n-1$, T_{b_n} is equal to the block temperature at time n , t_{interval} is a time in seconds between sample intervals, and τ is said first thermal time constant minus said second thermal time constant.

130. The method according to claim 128 wherein said sample block comprises a central region containing said at least one well, an end edge region in thermal contact with an enclosed ambient atmosphere and a manifold region thermally coupled to at least one manifold, wherein said heating means includes a zone for each of said regions, and wherein the step of controlling said heating means comprises the step of

(iv) determining a theoretical second power representing the total power to apply to said block in a current sample interval at a current time n without accounting for power losses,

(v) dividing said theoretical second power into theoretical powers, one to be applied to each of said heating zones,

(vi) determining power losses by said regions in said current sample interval, and

(vii) determining an actual third power for each of said zones in said current sample interval to account for power loss by each said zone.

131. The method according to claim 130 wher in said thermocycler additionally includes bias cooling constantly

applied to said sample block, wherein said computer-controlled cooling means comprises selectively operable ramp cooling means for selectively delivering a cooling fluid to said sample block, and wherein the step of controlling said selectively operable ramp cooling means includes the steps of

(viii) determining that sample temperature ramp direction is downward,

(ix) determining the temperature of said cooling fluid,

(x) determining as a function of said sample temperature a theoretical cooling power to apply to said block in said current sample interval without accounting for power losses,

(xi) determining a cooling breakpoint as a function of the difference between the block temperature and the temperature of said cooling fluid in the current sample interval, and

(xiii) selectively operating said ramp cooling means as a function of said theoretical cooling power and said cooling breakpoint.

132. Thermocycler apparatus suitable for automated performance of the polymerase chain reaction comprising

a. a metal sample block having a major top surface and a major bottom surface,

b. an array of spaced-apart sample wells formed in said major top surface,

7 c. bias cooling constantly applied to said sample block at a rate sufficient to cause said block, if at a temperature within the range of 35-100°C, to cool uniformly at a rate of at least about 0.1°C/sec unless external heat is supplied, and

12 d. computer-controllable heating means responsive to said computer system capable of uniformly raising the temperature of said block at a rate greater than the bias cooling rate, said thermocycler apparatus being capable, under the control of a
16 computer, of maintaining the array of sample wells at a constant in the range of 35-100°C within a tolerance band of plus or minus about 0.5°C.

133. Thermocycler apparatus according to claim 132 wherein said array comprises a rectangular array having rows of spaced-apart sample wells.

134. Thermocycler apparatus according to claim 133 wherein said array comprises an 8-by-12 rectangular array having center-to-center sample well spacing compatible with industry standard microliter plate format.

135. Thermocycler apparatus according to claim 134 wherein said sample block has a block thermal capacity of about 500-600 watt-seconds per °C.

136. Thermocycler apparatus according to claim 133 wherein said sample block contains multiple transverse bias cooling channels through said block parallel to said top surface and parallel to and spaced from the rows of wells, and wherein said bias cooling is applied by pumping cooling liquid through said bias cooling channels.

137. Thermocycler apparatus according to claim 136 wherein said bias cooling channels are insulated.

138. Thermocycler apparatus according to claim 132 wherein said computer-controllable heating means comprises multiple, separately controllable heating zones for said block, at least one first zone for the portion of the block containing the array of sample wells and at least one second zone for the peripheral portion of the block outside the array.

139. Thermocycler apparatus according to claim 138 wherein said computer-controllable heating means comprises a multizone film heater in thermal contact with said major bottom surface.

140. Thermocycler apparatus according to claim 132 wherein said sample block includes around its periphery a guard band having thermal characteristics similar to the block portion containing the array and wherein said guard band is bias cooled and controllably heated.

141. Thermocycler apparatus according to claim 140 wherein said guard band includes a groove formed in said top surface extending substantially around said array, decreasing the thermal conductivity between the block portion containing the array and the guard band.

142. Thermocycler apparatus according to claim 140 wherein said computer-controllable heating means comprises multiple, separately controllable heating zones for said block, at least one first zone for the portion of the block containing the array of sample wells and at least one second zone for the guard band.

143. Thermocycler apparatus according to claim 142 wherein said computer-controllable heating means comprises a multizone film heater in thermal contact with said major bottom surface.

144. Thermocycler apparatus according to claim 132 further comprising computer-controllable ramp cooling means capable of lowering the temperature of said block at a rate of at least about 4°C per second from 100°C and at least about 2°C per second from 40°C.

145. Thermocycler apparatus according to claim 144 wherein said array comprises a rectangular array comprising rows of spaced-apart sample wells, wherein said sample block contains multiple transverse bias cooling channels alternating with multiple transverse ramp cooling channels, and wherein said bias

cooling and said ramp cooling are applied by pumping cooling liquid through said ramp cooling channels and said bias cooling channels.

146. Thermocycler apparatus according to claim 145 further comprising means to deliver cooling liquid to opposite ends of successive ramp cooling channels.

147. Thermocycler apparatus according to claim 144 wherein said computer-controllable heating means is capable of ramp heating.

148. Thermocycler apparatus according to claim 147 wherein said controllable heating comprises multiple, separately controllable heating zones for said block, at least one first zone for the portion of the block containing the array of sample wells and at least one second zone for the portion of the block outside the array.

149. Thermocycler apparatus according to claim 148 wherein said computer-controllable heating means comprises a multizone film heater in thermal contact with said major bottom surface.

150. Thermocycler apparatus according to claim 132 further comprising means for seating into the wells in said array sample tubes of nonidentical height with a seating force on each sample

tube sufficient to cause a snug, flush fit between the surface of the tube and the surface of the well.

151. Thermocycler apparatus according to claim 150 wherein said means for seating comprises deformable, compliant, gas-tight caps for said sample tubes, a vertically displaceable platen, and controllable means for forcibly lowering said platen to maintain said seating force on the cap for each tube.

152. Thermocycler apparatus according to claim 151 wherein said platen is maintained at a heated temperature in the range of 94-110°C.

153. Thermocycler apparatus according to claim 152 wherein said platen is maintained at a temperature in the range of 100-110°C.

154. Thermocycler apparatus according to claim 132 further comprising a computer system for controlling said heating means.

155. Thermocycler apparatus according to claim 144, wherein said computer system controls said ramp cooling means.

156. Thermocycler apparatus suitable for automated, rapid performance of the polymerase chain reaction comprising

a. a thermally homogeneous metal sample block of low thermal mass having a major top surface and a major bottom

5 surface, said block containing in a central region of its upper surface an 8-by-12 rectangular array of sample wells having center-to-center spacing compatible with industry standard microliter plate format, said block also containing a peripheral region surrounding said array, said peripheral region comprising a guard band having thermal characteristics similar to the thermal characteristics of the central region,

b. a bias cooling system for constantly cooling said sample block at a bias cooling rate sufficient to cause said block, if at a temperature within the range of 35-100°C, to cool uniformly at a rate of at least about 0.1°C/sec unless external heat is supplied,

c. a computer system for receiving and storing user data regarding times and temperatures defining a plurality of reaction cycles,

20 d. a ramp cooling system controlled by said computer system for selectively cooling said sample block at a ramp cooling rate of at least about 4°C/sec from 100°C and at least about 2°C/sec from 40°C,

25 e. a multizone heating system controlled by said computer system having a heating zone for the central region of the block and a heating zone for the guard band, said heating system being capable of providing heat necessary to maintain the sample block at a constant temperature in the range of 35-100°C and also capable of providing ramp heating to the block,

30 f. a pressing cover vertically displaceable above said sample block, and

g. cover displacing means for raising said cover and for lowering said cover and maintaining its vertical position against a resisting force of at least about 3000 grams, 35 said thermocycler apparatus being capable of maintaining the array of sample wells at a constant temperature in the range of 35-100°C within a tolerance band of plus or minus 0.5°C.

157. Thermocycler apparatus according to claim 156 wherein said pressing cover comprises a heated platen maintainable at a temperature in the range of 94-110°C.

158. Thermocycler apparatus according to claim 156 wherein said multizone heating system comprises a film heater in thermal contact with the bottom surface of the sample block.

159. Thermocycler apparatus according to claim 158 wherein said bias cooling system comprises a series of bias cooling channels through said block parallel to said top surface and parallel to and spaced from the rows of wells, and pump means for pumping cooling liquid through said bias cooling channels.

160. Thermocycler apparatus according to claim 159 wherein said ramp cooling system comprises a series of ramp cooling channels through said block parallel to the bias cooling channels and spaced apart therefrom and from the rows of wells, and pump means for pumping cooling liquid through said ramp cooling

channels, entering at opposite ends of successive ramp cooling channels.

161. Thermocycler apparatus according to claim 160 wherein there is one bias cooling channel and one ramp cooling channel proximate each row of sample wells.

162. Thermocycler apparatus according to claim 156 further comprising

h. a two-piece plastic holder for loosely holding up to 96 microliter sample tubes of a preselected design, each having a cylindrically shaped upper section open at its top end and a closed, tapered lower section extending downwardly therefrom, each tube being of circular cross section and having a circumferential shoulder extending outwardly from said upper section at a position on said upper section spaced from the open end thereof, comprising

aa. a one-piece tray member comprising

- i. a flat, horizontal plate section containing 96 holes in an 8-by-12 rectangular array compatible with industry standard microliter plate format, said holes being slightly larger than the outside diameter of the upper sections of said tubes but smaller than the outside diameter of said shoulder,
- ii. a first vertical tray sidewall section completely around said plate extending

upwardly to a height greater than the height of a tube resting in one of said holes,
iii. a second vertical tray sidewall section around said plate extending downwardly approximately to the bottom of the upper section of a tube resting in one of said holes,

bb. a one-piece retainer releasably engageable inside said tray over any sample tubes resting in said tray comprising

- i. a flat, horizontal plate section containing 96 holes in an 8-by-12 rectangular array compatible with industry standard microliter plate format, said holes being slightly larger than the outside diameter of the upper sections of said tubes but smaller than the outside diameter of said shoulder,
- ii. a vertical retainer sidewall section around said retainer plate section extending upwardly from said plate,

wherein when said retainer is engaged inside said tray, the retainer plate section lies slightly above the shoulder of a tube resting in said tray and the first tray sidewall section is about as high as said retainer sidewall section, whereby tubes resting in said tray are retained loosely both vertically and laterally and extend downwardly into said sample wells,

- i. up to 96 microliter sample tubes in said holder, each of which engages a deformable cap for forming a gas-tight seal

thereon, and each of which said caps protrudes slightly above an uppermost edge of said two-piece plastic holder when said sample tubes are seated in said holder and in said sample wells.

163. Thermocycler apparatus according to claim 162 wherein the downward displacement of said cover deforms the tops of said caps downwardly until the displacement is stopped by said uppermost edge of said two-piece plastic holder.

164. Thermocycler apparatus according to claim 163 wherein said uppermost edge of said two-piece plastic holder contacts the underside of said cover around the entire periphery of said edge, thus forming a gas-tight seal.

165. Thermocycler apparatus according to claim 156 comprising at least two heating zones for the guard band.

166. A two-piece plastic holder for loosely holding up to 96 microliter sample tubes of a preselected design, each having a cylindrically shaped upper section open at its top end and a closed, tapered lower section extending downwardly therefrom, each tube being of circular cross section and having a circumferential shoulder extending outwardly from said upper section at a position on said upper section spaced from the open end thereof, comprising

- a. a one-piece tray member comprising
 - i. a flat, horizontal plate section containing 96 holes in an 8-by-12 rectangular array compatible with industry standard microliter plate format, said holes being slightly larger than the outside diameter of the upper sections of said tubes but smaller than the outside diameter of said shoulder,
 - ii. a first vertical tray sidewall section completely around said plate extending upwardly to a height greater than the height of a tube resting in one of said holes,
 - iii. a second vertical tray sidewall section around said plate extending downwardly approximately to the bottom of the upper section of a tube resting in one of said holes,
- b. a one-piece retainer releasably engageable inside said tray over any sample tubes resting in said tray comprising
 - i. a flat, horizontal plate section containing 96 holes in an 8-by-12 rectangular array compatible with industry standard microliter plate format, said holes being slightly larger than the outside diameter of the upper sections of said tubes but smaller than the outside diameter of said shoulder,

- ii. a vertical retain r sidewall section around
said retainer plate section extending
upwardly from said plate,

wherein when said retainer is engaged inside said tray, the
retainer plate section lies slightly above the shoulder of a tube
resting in said tray and the first tray sidewall section is about
as high as said retainer sidewall section, whereby tubes resting
in said tray are retained loosely both vertically and laterally.

167. Apparatus according to claim 166 wherein the holes in
said tray section are countersunk and wherein the underside of
the shoulders of said tubes are correspondingly beveled.

168. Apparatus according to claim 167 wherein the holes in
the tray plate section and in the retainer plate section are
larger in diameter than said tubes by about 0.7 mm.

169. Apparatus according to claim 166 wherein said tray
member further comprises a plurality of support ribs extending
along the underside of the tray plate member between rows of
holes said ribs extending downwardly to the same extent as said
second vertical tray sidewall section.

170. Apparatus according to claim 166 wherein said tray
member further comprises a skirt section extending at least
partially around said tray plate section and depending vertically

from that section, said skirt section being adapted to fit into a guard band groove in a thermocycler sample block.

171. Apparatus according to claim 166 wherein said tray plate section has at least two openings provided therein and said retainer plate section has an identical number of vertical tabs, downwardly extending from said retainer plate, such that said tabs project through said openings and releasably engage the tray when said retainer is assembled with said tray.

172. Apparatus according to claim 171 wherein said tabs are disposed so as to form part of a skirt section extending downwardly at least partially around said tray plate section and wherein said tabs are adapted to fit into a guard band groove in a thermocycler sample block.

173. Apparatus according to claim 172 wherein said openings and said tabs are positioned such that said retainer and said tray are capable of only one orientation relative to one another when said openings and said tabs are engaged.

174. Apparatus according to claim 171 wherein said tabs are deflectable in a sidewise direction in order to come into alignment with said openings.

175. Apparatus according to claim 166 further comprising up to 96 microliter sample tubes in said holder.

176. Apparatus according to claim 175 further comprising up to 96 deformable caps on said tubes for forming gas-tight seals thereon.

177. Apparatus according to claim 176 wherein each said cap has a downwardly depending cylindrical flange for forming a gas-tight seal with each said tube and a circumferential shoulder extending outwardly from said flange which prevents said flange from being seated on said tube below a predetermined point.

178. Apparatus according to claim 177 wherein the outer circumference of said downwardly depending flange fits snugly to form a gas-tight seal with the inner circumference of said tube.

179. Apparatus according to claim 176 wherein groups of 12 of said caps are linked together to form a single strand of caps which are suitably spaced so as to form gas-tight seals with up to 12 of said tubes.

180. Apparatus according to claim 166 further comprising a plastic base having 96 wells arranged in an 8-by-12 rectangular array, said wells being dimensioned to snugly accept the lower sections of up to 96 said sample tubes, said base being assemblable with said tray, said retainer and 96 of said tubes to form a microliter plat having the footprint of an industry standard microliter plate.

181. Apparatus according to claim 176 wherein said caps project above said first vertical tray sidewall section but are downwardly deformable to the height of said section.

182. Apparatus according to claim 181 wherein said caps are deformable by heat and vertically downward force.

183. Apparatus according to claim 181 wherein said caps are resiliently deformable.

184. A PCR reaction-compatible one-piece plastic microcentrifuge-type tube comprising a first substantially cylindrically shaped upper wall section and a second substantially conically shaped lower wall section characterized by said second wall section being substantially reduced in thickness relative to said first wall section to a thickness of no more than approximately 0.012 inches.

185. The tube of claim 184 wherein said second wall section comprises the frustrum of a cone with an included angle of about 17 degrees.

186. The tube of claim 185 wherein said second section holds about 100 microliters of liquid.

187. The tube of claim 184 wherein said first wall section has a thickness of about 0.03 inches.

188. The tube of claim 184 wherein said second wall section has a thickness of about 0.009 inches.

189. The tube of claim 184 wherein said tube is made from polypropylene.

190. The tube of claim 189 wherein said tube is autoclavable.

191. The tube of claim 189 wherein said second wall section has a thickness of about 0.009 inches.

192. The tube of claim 184 further comprising a one-piece cap pivotally attached to said tube and removably insertable into said tube to hermetically seal it, said cap comprising a substantially cylindrically shaped third lower section, a resiliently deformable closed fourth top section, and a circumferential shoulder, extending radially outwardly, attached to said third section.

193. The cap of claim 192, wherein said fourth section is dome shaped.

194. The cap of claim 192, wherein said cap is made from polypropylene.

195. The cap of claim 194, wherein said cap is autoclavable.

196. A PCR reaction-compatible five-hundred microliter microcentrifuge-type tube having an overall height of about 1.1 inches, comprising a substantially cylindrically shaped upper wall section and a substantially conically shaped lower wall section, characterized by said lower wall section including an angle of about 17 degrees and having a thickness substantially reduced relative to said upper wall section to approximately 0.012 inches.

197. The tube of claim 196 wherein said tube is made from polypropylene.

198. The tube of claim 197 wherein said tube is autoclavable.

199. A PCR reaction-compatible, one-piece molded plastic sample tube comprising

a first wall portion having a thickness of from about 0.008 to about 0.013 inches defining an inverted, substantially conically shaped lower section having a closed bottom end and an upper end approximately 0.2 inches in inside diameter, said lower section having a volume of about 100 microliters, and

a second wall portion, substantially thicker than said first wall portion, defining a substantially cylindrically shaped upper section approximately 0.2 inches in inside diameter, said upper section having a volume of at least about 100 microliters.

200. A tube according to claim 199 wherein said plastic is autoclavable.

201. A tube according to claim 199 wherein said first wall portion comprises the frustrum of a cone with an included angle of about 17 degrees.

202. A tube according to claim 199 wherein said plastic is polypropylene.

203. A tube according to claim 202 wherein said first wall portion has a thickness of about 0.009 inches.

204. A tube according to claim 199 wherein said tube comprises a top, further comprising a circumferential shoulder extending radially outwardly from said second wall portion, said shoulder being spaced from said top.

205. A tube according to claim 204 wherein said shoulder has a beveled lower portion.

206. A tub according to claim 205 wherein said first wall portion has a thickness of about 0.009 inches, wherein said plastic is autoclavable polypropylene, and wherein said first wall portion comprises the frustrum of a cone with an included angle of about 17 degrees.

207. A tube according to claim 206 wherein said second wall portion is outwardly thickened at said top.

208. A tube according to claim 207 wherein the inside surface of said second wall portion is beveled at said top.

209. The apparatus of any of claims 1, 132, 156 or 166 further comprising at least one tube according to claim 184, wherein substantially entirely said second wall section contacts the wall of a well.

210. The apparatus of any of claims 1, 132, 156 or 166 further comprising at least one tube and cap according to claim 192 wherein substantially entirely said second wall section contacts the wall of a well.

211. In a combination of a thermal cycler suitable for performing the polymerase chain reaction comprising a temperature-controlled metal block having an array of tapered wells in its top surface, and a plurality of individual reaction tubes having similarly tapered lower sections and upper sections

which project above the top surface of the block when the tubes are placed in said wells, the improvement comprising means for seating said tubes in said wells, said seating means comprising:

10 a) resiliently deformable sealing caps removably attached to said tubes,

b) a platen,

c) support means for supporting the platen above the block,

15 d) displacement means associated with the support means for raising the platen above said caps and for lowering it so as to apply a force of at least 30 grams to each cap.

212. The apparatus according to claim 211 further comprising controllable heating means to maintain said platen at a preselected temperature in the range of 94-100°C.

213. The apparatus according to claim 212 further comprising skirt means attached to said support means for isolating said block and said tubes.

214. The apparatus according to claim 212, wherein said displacement means comprises screw means.

215. The apparatus according to claim 212 further comprising a two-piece plastic holder according to claim 166, wherein each said tube has a circumferential shoulder extending outwardly from said upper section at a position on said upper section below the

open end thereof, and wherein said array of tapered wells comprises 96 wells in an industry standard microtiter plate format.

216. The apparatus according to claim 215, wherein said displacement means includes means for lowering said platen so as to apply a force of 50-100 grams to each cap.

217. The apparatus of claim 215, wherein said displacement means further comprises means for seating said platen on said uppermost edge of said holder such that said tubes are substantially enclosed by the block, the uppermost edge of said holder and the platen.

218. The apparatus of claim 211, wherein said plurality of reaction tubes are loosely held in an array.